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Research Article

Secondary Osteoporosis in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

Osteoporosis in patients with broncho-pulmonary pathology is associated with the fact that the inflammatory process has a direct effect on bone metabolism. A large number of pro-inflammatory cytokines, which play an important role in the pathogenesis of obstructive pulmonary diseases, is involved in the regulation of bone resorption. In addition, patients with chronic obstructive pulmonary disease (COPD) of severe and extremely severe degrees, according to GOLD recommendations, receive inhaled glucocorticosteroids (GCS), and in ineffective inhaled GCS-therapy COPD patients are prescribed systemic steroids; that has an undesirable effect on bone marrow state.

The purpose of the work was to investigate the peculiarities of bone metabolism disorders in patients with COPD. There were examined 26 patients with COPD of the III-IV degrees, groups C and D aged 65.3±3.15 years. Spirography, bone mineral density study were performed; ten-year risk of osteoporotic fractures was evaluated using FRAX; content of calcium, phosphorus, alkaline phosphatase in blood serum were determined.

As a result of laboratory studies and densitometry, 84.6% of patients were diagnosed osteopenia. The average T-criterion was within (-1.83±0.17) SD (standard deviation) and was significantly lower than in healthy persons (-0.56±0.10) SD, ($p<0.001$). The degree of reduction of bone mineral density depended on the degree of reduction of FEV1 and COPD degree ($r=0.65$; $p<0.01$), as well as on the duration of the disease ($r=-0.43$; $p<0.01$). The ten-year risk of osteoporotic fractures in patients with COPD was high and was 5.65%±1.63%, as opposed to 2.13%±0.61% ($p<0.001$) in practically healthy individuals.

Thus, severe functional disorders in COPD, a durable anamnesis of the disease contribute to a decrease in bone mineral density and to an increase in the risk of osteoporotic fractures.

Keywords

chronic obstructive pulmonary disease; osteoporosis; osteopenia

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Problem statement and analysis of the latest research

Osteoporosis is a systemic disease of the skeleton, which is characterized by a decrease of bone mass, a violation of the micro-architectonics of bone tissue, which leads to the increased bone fragility and the risk of fractures [1].

Among the risk factors for osteoporosis the unmodified (genetic), modified factors, and medication influence can be identified. On the one hand, the role of hereditary predisposition to this disease is incontrovertible; on the other hand – the value of such "exogenous" risk factors as deficiency of protein, calcium, vitamin D, smoking, alcohol abuse, hypodynamia, low body mass, early menopause in women is firmly proven. [7, 10]. Among the diseases that contribute to the development of osteoporosis, a special place belongs to the chronic obstructive pulmonary disease (COPD). This is due

to the commonality of many exogenous risk factors for the development of osteoporosis and COPD, mechanisms of pathogenesis, and the influence of medicines used in the treatment of COPD [2, 4].

Osteoporosis in patients with broncho-pulmonary pathology belongs to the category of secondary ones. It is associated with the fact that the inflammatory process has a direct effect on bone metabolism. A large number of pro-inflammatory cytokines, playing an important role in the pathogenesis of obstructive pulmonary disease, is involved in the regulation of bone resorption. Tumor necrosis factor-α contributes to the increase of number and maturation of osteoblasts [8]. Interleukin-1 (IL-1) and interleukin-6 (IL-6) are powerful mediators of osteoclastogenesis (according to in vitro, IL-1 is a 4-fold stronger factor in bone resorption than parathyroid hormone). Thus, the effect of these and other cytokines, including IL-11 and monocyte-macrophage colony-stimulating factor, is explained by the relationship between the inflammatory process in the broncho-pulmonary system, bone remodeling, and loss of bone mass [2, 10].

In addition, patients with COPD of severe and extremely severe degrees, according to GOLD recommendations, receive inhaled glucocorticosteroids (GCS) as the part of basic therapy. The proven systemic effects, developing in response to the use of high doses of inhaled GCS (over 1000 micrograms per day for beclomethasone dipropionate and over 750 micrograms per day for fluticasone), include osteoporosis in adults and the effect on linear growth in children [3, 5, 9].

When glucocorticoid therapy is ineffective, patients with COPD are sometimes prescribed systemic GCS; it also has an undesirable effect on bone tissue metabolism. Meta-analysis of the results of controlled studies has shown that the appointment of even minimal (2.5 mg/day) doses of GCS may have an adverse effect on bone state. The highest loss of bone tissue develops during the first 6-12 months of GCS-therapy [2]. The main peculiarity of steroid osteoporosis – is the effect of GCS on both processes underlying remodeling of bone tissue: decrease of osteoblast-mediated formation and increase of osteoclast-mediated bone resorption. Additional factors in this process are the reduction of the synthesis of collagen and non-collagen proteins, as well as local factors of bone tissue growth (insulin-like growth factor-1, transforming growth factor, etc.) [4, 6].

It should be emphasized that osteoporosis in patients with COPD also develops in the absence of GCS-therapy. Among patients with COPD with FEV1 below 80% of the appropriate, who have never received GCS, osteoporosis (according to T-criterion) was registered 4 times more than in the control group. Vertebral fractures were observed in 12.4% of patients with COPD with moderate functional impairment (FEV1 is 70% of appropriate), who did not receive GCS [6, 7].

Objective: to investigate the peculiarities of bone metabolism disorders in patients with chronic obstructive pulmonary disease.

1. Materials and Methods

There were examined 26 patients with COPD of the III-IV degree, groups C and D and 12 practically healthy persons. The average age of patients was 65.3$\pm$3.15 years. Among the examined patients, 18 (69.2%) men had COPD of the III degree; 8 (30.8%) – had COPD of the IV degree. In 14 (53.8%) patients group C was determined, and in 12 (46.2%) – group D of this disease. To confirm the diagnosis of COPD, patients were performed a clinical, laboratory and instrumental examination in accordance with the Order of the Ministry of Health of Ukraine #555 dated June 27, 2013; and according to International Recommendations GOLD-2017. The treatment schemes included inhaled GCS as basal medicines, and 12 (46.2%) patients received systemic GCS [1, 5]. Investigation of bone mineral density (BMD) was performed using an X-ray densitometer "CHALLENGER" with an evaluation of the results according to the T-criterion in standard deviations (SD) from bone mass. The ten-year risk of osteoporotic fractures was calculated using the FRAX computer program. The content of calcium, phosphorus, alkaline phosphatase in blood serum was studied. Patients provided informed consent to participate in the clinical trial. Statistical processing

of indicators was carried out using the application package of computer programs Statistica 7.

2. Results and Discussion

In the course of the study, it was found that most patients with COPD complained of coughing with purulent sputum discharge, shortness of breath. 21 (80.8%) patients in the anamnesis pointed to smoking, and 4 patients (15.4%) – for the presence of data on the impact of occupational hazards. The majority of patients had classic objective signs of COPD, 18 patients (69.2%) were diagnosed signs of decompensated pulmonary heart. Spirographic parameters corresponded to the broncho-obstruction degree and the degree of COPD. Laboratory indices of exchange of calcium and phosphorus did not differ significantly from indicators in healthy individuals (see Fig. 1).

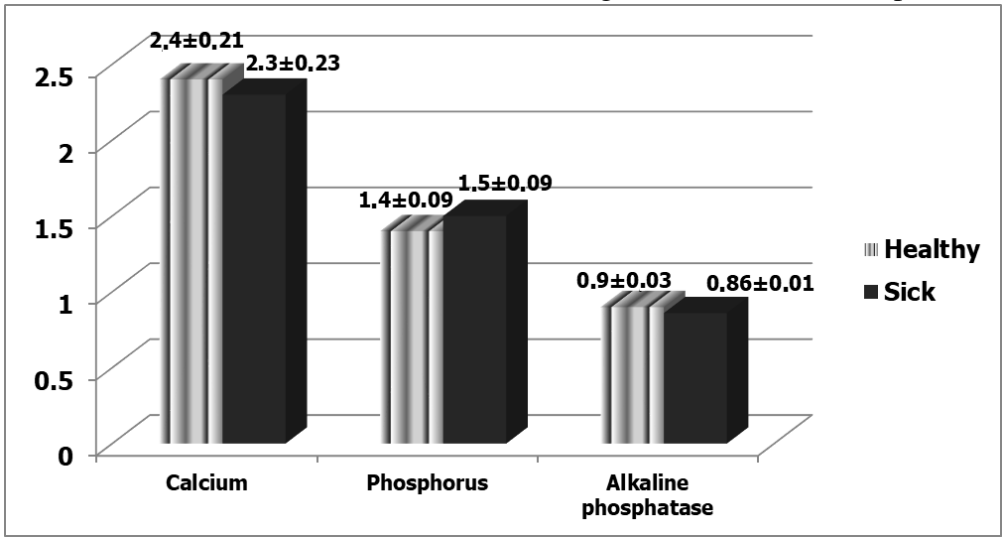

Figure 1. Laboratory indices of calcium metabolism in the examined patients.

Results of densitometry of the lumbar spine L2-L4 are represented in Fig. 2. The average indicators of the T-criterion were within (-1.83±0.17) SD and were significantly lower than in healthy persons (-0.56±0.10) SD ($p<0.001$). As it is known, in COPD the treatment with GCS has a negative influence not only on "quantity" (mineral density of bone tissue), but also on "quality" of bone. This leads to the fact that the "threshold of fracture" in patients receiving GCS is lower than in those who do not take these medicines. That is why in most cases, steroid osteoporosis is diagnosed according to the T-criterion of osteo-densitometry not at 2.5, but at 1.5 standard deviations (SD) from the peak bone mass of persons of the corresponding gender [2]. The peculiarity of steroid osteoporosis is a more pronounced lesion of the trabecular (spine, trochanter major) than of the cortical (long bones) bone tissue [6].

Osteopenia was diagnosed in 22 (84.6%) patients. The degree of reduction in mineral density of bone tissue depended on the degree of reduction of FEV1 and the degree of COPD ($r=0.65$; $p<0.01$).

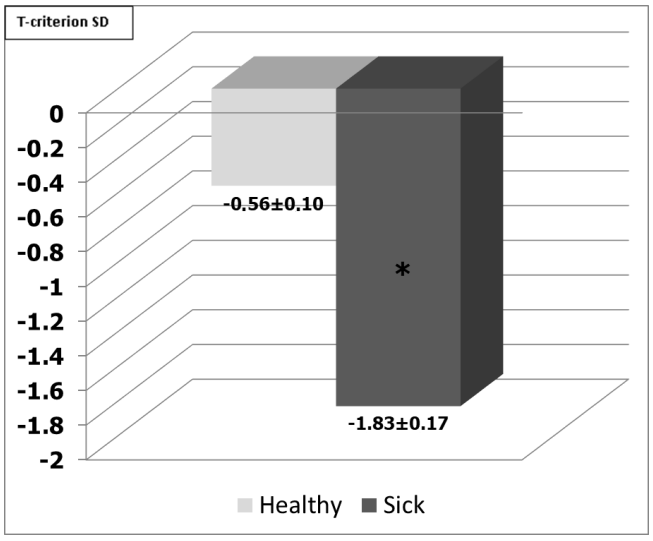

Figure 2. Results of densitometry in the examined patients. *Note: Statistical significance of differences from healthy persons * $p<0.001$*

The inverse correlation relationship was found between the index of bone mineral density and the duration of the disease ($r=-0.43$; $p<0.01$).

The ten-year risk of osteoporotic fractures in patients with COPD was high and was $5.65\%\pm1.63\%$, as opposed to $2.13\%\pm0.61\%$ ($p<0.001$) in practically healthy individuals. As it is known, the relative risk of fractures of the skeletal bones (spine, femoral bone) increases with the dose-dependent GCS [6, 9].

3. Conclusions

1. Based on the performed studies, it was found that more than 80% of patients with COPD of the III-IV degree, groups C and D have osteopenia.

2. Severe functional disorders in COPD, a durable anamnesis of this disease contribute to a decrease in mineral density of bone tissue and an increase of the risk of osteoporotic fractures.

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